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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,544	10/29/2003	Anthony W. Confer	57188/02-774	7788

22206 7590 06/28/2005

FELLERS SNIDER BLANKENSHIP
BAILEY & TIPPENS
THE KENNEDY BUILDING
321 SOUTH BOSTON SUITE 800
TULSA, OK 74103-3318

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,544	CONFER ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *4-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4.1.05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 04/11/05 in response to the non-final Office Action mailed 12/30/04. With this, Applicants' have amended the specification.

Status of Claims

2) Claims 1 and 3-5 have been amended via the amendment filed 04/11/05.

Claims 1-8 are pending.

Claims 1-3 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the Oath/Declaration made in paragraph 5 of the Office Action mailed 12/30/04 is withdrawn in light of Applicants' submission of a new Oath/Declaration.

6) The objection to the specification made in paragraph 7 of the Office Action mailed 12/30/04 is withdrawn in light of Applicants' amendments to the specification.

Rejection(s) Withdrawn

7) The rejection of claims 1 and 3 made in paragraph 9(a) of the Office Action mailed 12/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

8) The rejection of claim 3 made in paragraph 9(b) of the Office Action mailed 12/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of

Applicants' amendment to the claim.

9) The rejection of claims 2 and 3 made in paragraph 9(c) of the Office Action mailed 12/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) Maintained

10) The rejection of claims 1-3 made in paragraph 11 of the Office Action mailed 12/30/04 under 35 U.S.C § 102(b) as being anticipated by Pandher *et al.* (*Infect. Immun.* 66: 5613-5619, December 1998 – Applicants' IDS) as evidenced by Hunter (US 5,554,372) or Berinstein *et al.* (US 20040033234), is maintained for reasons set forth therein and herebelow.

Applicants contend that: (a) Pandher *et al.* did not produce recombinant PlpE in its pure form, and did not immunize calves with it; (b) Pandher *et al.* merely showed that cattle that recovered from previous *M. haemolytica*-induced disease or experimentally vaccinated with the entire outer membrane from the bacterium developed antibodies to PlpE; (c) Pandher *et al.* used the PlpE expressed on the surface of *E. coli* to purify those antibodies and show that they could kill the bacterium in the presence of complement; (d) Calves were never vaccinated with PlpE or challenged with *M. haemolytica* to demonstrate that this protein had potential vaccine properties; (e) The term 'recombinant' is used loosely in Pandher's paper; (f) Pandher *et al.* use the phrase 'recombinant *E. coli*' several times when they might better have said an *E. coli* host expressing PlpE on its surface 'as an integral part of its outer membrane'; (g) Pandher *et al.* use such an *E. coli* to absorb antibodies specific to PlpE from a convalescent serum obtained from a calf with *M. haemolytica* or serum generated by immunizing animals with outer membrane proteins of the same organism to a state where complement-mediated cell killing activity was reduced significantly; (h) Pandher *et al.* (1998) can be considered nothing more than an invitation to try; (i) Antibodies against PlpE that were used by Pandher *et al.* (1998) were those that were affinity purified from a calf's serum; (j) That calf had been vaccinated with the entire outer membrane of *M. haemolytica* (*M. haemolytica* was called *Pasteurella haemolytica* at that time), which contains at least 21 different immunogenic outer membrane proteins - of which P1pE is only one (Pandher K, Murphy GL, Confer AW., Identification of immunogenic, surface-exposed outer

membrane proteins of *Pasteurella haemolytica* serotype 1. *Veterinary Microbiology* 65: 215 - 226, 1999, previously submitted under IDS of July 7, 2004); (k) Pandher *et al.* (1998) used that serum in an *in vitro* complement-mediated killing assay before and after antibodies to P1pE were removed by adsorption to PlpE expressed on the surface of *E. coli*; (l) They showed that removal of the antibodies to PlpE eliminated complement-mediated killing of *M. haemolytica* and in their discussion state "[r]esults of the complement-mediated killing assays demonstrate that ant-PlpE contribute to this mechanism of bovine defense, one that is believed to be important in protection against *P. haemolytica*." Therefore, Pandher *et al.* (1998) demonstrated only indirectly and by *in vitro* laboratory test that there was a potential for antibodies to *M. haemolytica* to be protective against the bacterium. Again, they did not vaccinate cattle and demonstrate directly that PlpE induced protection. In fact, other potential immune mechanisms that occur in cattle when exposed to a pathogenic agent, like *M. haemolytica*, were not investigated. These include: cell-mediated cytotoxicity; opsonization, phagocytosis and killing; antibody-dependent cytotoxicity; and activation of natural killer cells. Thus, only one of several important mechanisms of host defense was addressed in a single in vitro experiment leaving a reader with the question of how relevant are these data to protection of cattle from *M. haemolytica* infection; (m) In the Discussion section of Pandher *et al.* (1998), the DNA sequence identities and similarities between P1pE and *Actinobacillus pleuropneumoniae* OMIA serotypes are compared; (n) Even though there are similarities between sequences from *M. haemolytica* and *A. pleuropneumonia*, those similarities were not great and consist of only 18-20% identity and 32 - 35% similarity between PlpE and Om1A from *A. pleuropneumonia* serotypes 1 and 5; (o) They further described that in vaccination experiments conducted by others with recombinant *A. pleuropneumoniae* Om1A the recombinant protein "...significantly reduced lung damage and death of pigs upon subsequent experimental challenge." They then commented that "...P1pE may have potential for being a significant cross-protective antigen. ..", and that "[f]uture studies will be necessary to evaluate the capacity of P1pE to enhance protection of cattle against experimental challenge."; (p) Those statements were all that were made theoretically linking PlpE with a vaccine. Pandher *et al.* did not use recombinant PlpE as a vaccine in any form and only showed indirectly that it had any vaccine potential through *in vitro* complement-mediated

killing and inference from publications from a related bacterium - *A. pleuropneumoniae*; (q) Pandher *et al.* also makes no mention of the potential use of PlpE as an addition to an existing *M. haemolytica* vaccine. Consequently, Pandher *et al.* cannot be said to anticipate Applicant's claimed invention.

Applicants further submit the following arguments: (i) In the present case, recombinant PlpE was expressed in *E. coli* BL21 (DE3) pLysS and purified on a nickel affinity column and used to vaccinate calves; (ii) The response of the animals was determined by measuring circulating anti-PlpE antibodies on ELISA and Western blots in which purified recombinant PlpE was used as ligand; (iii) The protective nature of the specific immune response was demonstrated by challenging the calves with live homologous *M. haemolytica* strain and bactericidal activity of an anti-plpE hyperimmune serum in the presence of a complement; (iv) Applicants demonstrated directly the immunogenic nature of recombinant PlpE and its potential as vaccine or component of a commercial vaccine. Thus, recombinant PlpE is used herein in the conventional sense, referring to purified PlpE from the *M. haemolytica* PlpE gene over-expressed in the expression host and purified.

Applicants' arguments have been carefully considered, but are not persuasive. Those arguments of Applicants' with regard to Pandher's teachings that are relevant to the rejection of record are responded to herebelow. As set forth in paragraph 11 of the Office Action mailed 12/30/04, the term 'vaccine' represents the intended use of the claimed protein and therefore has no patentable weight. To qualify as art under 35 U.S.C § 102, Pandher *et al.* do not have to teach *M. haemolytica* recombinant PlpE in its pure form, because the instantly recited recombinant PlpE outer membrane protein in the claimed composition is not required to be 'purified'. Therefore, Pandher's recombinant PlpE outer membrane protein of *P. haemolytica* expressed on the surface of *E. coli* and comprising the amino acid sequence of SEQ ID NO: 2, or Pandher's entire outer membrane of *M. haemolytica* comprising PlpE as one OMP is not excluded from the scope of the instant claims. Irrespective of whether or not Pandher *et al.* use the phrase 'recombinant *E. coli*' as opposed to an *E. coli* host expressing PlpE on its surface 'as an integral part of its outer membrane', Pandher's composition anticipates the instantly claimed composition. Pandher *et al.* clearly taught a composition comprising PBS (i.e., a

pharmaceutically acceptable carrier or diluent) and a recombinant PlpE outer membrane protein of *P. haemolytica* comprising the amino acid sequence of SEQ ID NO: 2 (see abstract; Materials and Methods; Figures 1 and 2; and Results). Pandher's PlpE is taught to be immunogenic in cattle (see abstract). Pandher's recombinant PlpE outer membrane protein of *P. haemolytica* having the amino acid sequence of SEQ ID NO: 2 and being comprised in PBS inherently serves as a vaccine composition. Since the claims under examination are not directed to a method of immunization of calves, Pandher *et al.* do not have to teach immunization of calves with their composition. A sequence search performed at the Office demonstrated that the prior art amino acid sequence has 100% sequence identity with the instantly recited recombinant *M. haemolytica* PlpE outer membrane protein of SEQ ID NO: 2. See the sequence search report attached to the Office Action mailed 12/20/04. Although the prior art does not refer to the protein as the recombinant PlpE of '*M. haemolytica*', because of its structural identity with the prior art protein, the instantly recited protein of SEQ ID NO: 2 is viewed as the same as the prior art *P. haemolytica* recombinant PlpE, but named differently as recombinant PlpE of '*M. haemolytica*'. In fact, Applicants acknowledge that *M. haemolytica* was previously called *Pasteurella haemolytica*. See line 9 on page 16 of Applicants' response filed 04/11/05. Pandher's recombinant *E. coli* PlpE composition is viewed as inherently containing an adjuvant since: (a) *E. coli* is well known in the art to be a Gram negative bacterium which contains the lipoplysaccharide antigen as a part of its cell, and (b) the lipopolysaccharides have been well known in the art to serve as intrinsic adjuvants. For example, see first paragraph under Example 17 of Hunter; and section [0097] of Berinstein *et al.* Thus, claims 1-3 are anticipated by Pandher *et al.* Hunter or Berinstein *et al.* is **not** used as a secondary reference in combination with Pandher *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Pandher *et al.* with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978).

As Applicants readily acknowledge, Pandher *et al.* vaccinated a calf with the entire outer membrane of *M. haemolytica*, called *Pasteurella haemolytica* at that time, containing PlpE. By showing complement-mediated killing of *M. haemolytica* by anti-PlpE antibodies, Pandher *et al.* provided the *in vitro* data correlative of protection. As acknowledged by Applicants, Pandher *et*

al. (1998) then used serum from the vaccinated calf in an *in vitro* complement-mediated killing assay before and after antibodies to PlpE were removed by adsorption to PlpE expressed on the surface of *E. coli.* Pandher *et al.* (1998) thus showed that removal of the antibodies to PlpE eliminated complement-mediated killing of *M. haemolytica* and concluded that '[r]esults of the complement-mediated killing assays demonstrate that ant-PlpE contribute to this mechanism of bovine defense, one that is believed to be important in protection against *P. haemolytica.*' Thus, via *in vitro* complement-mediated killing assay that is correlative of protection against *M. haemolytica*, Pandher *et al.* (1998) have showed that their composition serves as a vaccine composition. The rejection stands.

Remarks

11) Claims 1-3 stand rejected.

It is noted that claim 1 includes an incorrect or redundant limitation: 'of thereof' in line 4.

12) **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which center receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Central Fax number for submission of amendments, response or documents is (703) 872-9306.

14) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (51) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

June, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER